Cell

Molecular Movies… Coming to a Lecture near You

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Scientific visualizations are powerful tools for communicating the intricacies of cellular and molecular structures and dynamics. There is a disconnect, however, between the research data sets we seek to represent and the kinds of animation that allow us to visualize and communicate them. Scientists are increasingly turning to 3D animation software borrowed from the entertainment industry to import, animate, and even create simulations of their data.

Molecular visualization is our only tangible link to objects that are, by their very nature, "unseeable," that is, smaller than the wavelengths of visible light. Downloading and inspecting images of biomolecules is now commonplace, thanks to the advent of free, desktop-based molecular graphics tools. Indeed, it is difficult to imagine a molecular environment without instantly conjuring up pictures of the standard molecular graphics representations used in these programs. While we zoom, rotate, pan, hide, reveal, and color pieces of structures to probe their meaning, we sometimes forget that an image of a molecule on our screen is, by definition, a two-dimensional (2D) representation of a 3D object, an interpretation, a visual hypothesis (Frankel, 2008). Indeed, the standard molecular representations for proteins are effective if incomplete ways of focusing our attention on specific aspects of a structure. Each representation succeeds by withholding certain information from the viewer—information that is not critical to our understanding of those aspects of the structure we wish to examine. Even the data sets upon which most of us rely to "interact" with structures visually—such as Protein Data Bank (PDB) files or electron microscopy (EM) maps—are only models of the underlying experimental information. And yet, despite being several steps removed from the unadulterated data, our understanding of the molecular world has been transformed by such visual representations. It is through visual inspection of formalized "ribbon" representations emphasizing secondary structures that we came to recognize the shared folds and domains of proteins (Richardson et al., 1976). Molecular images empower us to communicate data that are otherwise too complex to process in the mind's eye.

Having accumulated over 50,000 structures through X-ray, NMR, and EM techniques, biologists are also beginning to probe the dynamics of macromolecules in more powerful ways. The availability of structures for multiple conformational sub-states of a protein whets our appetite to visualize how the protein might morph between these states. It is now possible to examine directly how a protein's conformational flexibility affects its function during catalysis (Henzler-Wildman et al., 2007). Moreover, increased computational power and new algorithms are beginning to address the behavior of larger molecular assemblies over longer timescales (Maragakis et al., 2008; Sotomayor and Schulten, 2007; Karplus and Kuriyan, 2005). Similarly, recent improvements in the spatial resolution of electron cryotomography allow us to probe the structure, location, and composition of molecular machines within large swathes of the cellular landscape (Robinson et al., 2007).

The insights emerging from these various new avenues of structural cell and molecular biology call for more sophisticated visual renderings. For decades, we have used mostly static representations of proteins outside of their cellular context that lack a critical layer of kinetic information. Proteins are dynamic shape-shifting entities that are constantly exploring the thermodynamic landscape available to them. Their association and dissociation from partner proteins involve a range of conformational states that are critical to their function. We need to incorporate this information into workable models that can be communicated to others. Unfortunately, it is these very aspects of structure that our existing software tools do not permit us to visualize readily. Scientists are finding that the entertainment industry's 3D software development efforts aimed at creating special effects and animated feature films provide powerful platforms for data visualizations. Indeed, the very same tools that were invented to animate a character like Shrek or Nemo are now being applied to set in motion protein domains and cellular processes. Although there is a disconnect between PDB files (and other data sets) and existing animation tools in molecular graphics packages, 3D animation software from Hollywood is poised to bridge that gap. This Commentary discusses some of the challenges inherent to cell and molecular visualization and explores how 3D software is helping to overcome these challenges.

Challenges in Visualization

The measure of any visualization, static or animated, continues to be how well it conveys pertinent information. What information to include depends on the target audience and communication

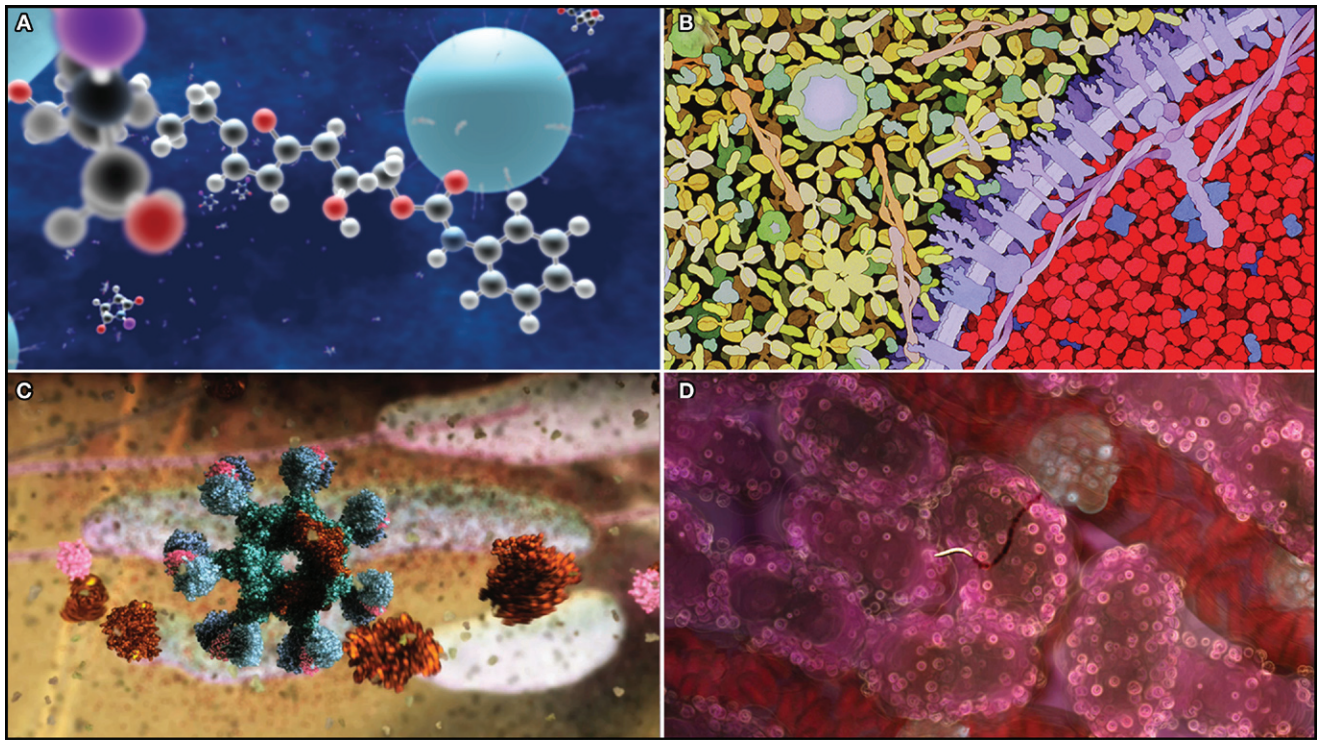

Figure 1. "Immersive" versus "Cross-Section" Visual Metaphors

Two common approaches to representing the cellular or molecular world depend on camera placement, which influences what characteristics are highlighted. (A and C) Immersive representations place the camera (and therefore the viewer) within the environment and are common in "fly-through" type sequences. (B and D) Cross-section representations distance the camera from a visual "slice" through the environment and can be used to depict, for example, macromolecular crowding.

(A) An immersive animation describing Stuart Schreiber's diversity-oriented chemical synthesis process (http://www.bloopatone.com/quicktimes/fold.mov). Figure courtesy of Eric Keller.

(B) A still image uses a cross-section through part of an erythrocyte cytosol to depict its crowded molecular interior and extracellular space (http://mgl.scripps.edu/people/goodsell/). Figure courtesy of David Goodsell.

(C) An immersive animation depicting the death receptor signaling pathway and ensuing caspase cascade (http://www.molecularmovies.com/movies/berry_apoptosis.html). Figure courtesy of Drew Berry.

(D) A frame from a 3D animation on the lifecycle of malaria shows a section through the liver with the parasite in yellow. (http://www.molecularmovies.com/movies/berry_malariaV4.html). Figure courtesy of Drew Berry.

goals. Several characteristics of molecular and cellular environments require us to develop distinct visual metaphors for their representation. For example, the first decision in "shooting" a virtual picture or movie is to decide where to put the camera. Cell and molecular environments are extremely crowded, and we are usually left with one of two choices for their visual representation: immersive metaphors versus cross-section metaphors (Figure 1). In the former, the camera (and therefore viewer) is part of the environment, whereas in the latter, it stays at a distance and observes a virtual "section" through the environment. Each has its benefits and pitfalls. Immersive representations typically require that we decrease the concentration to allow for depth of field. The virtual camera can travel through vast vistas that serve as better canvases for depicting binding and dissociation of components (Figures 1A and 1C). On the other hand, cross-section representations, whether in static pictures (Figure 1B) or animations (Figure 1D), can be great tools to depict molecular crowding. This technique is usually used at the expense of depth perception. Which metaphor is better? As with any visualization, it depends entirely on the audience and goal of your images. One of the more powerful aspects of animation is that one may transition between these different visual metaphors during the course of a single movie.

Depicting a wide continuum of scale (from atomic level reactions to cellular ultrastructure) is another important challenge. Because the effect of a single bond rearrangement can influence the structure of an entire protein complex, we face the task of selecting meaningful molecular representations at each end of the size spectrum. This property sometimes calls for mixed visual metaphors (such as a stick model surrounded by a semitransparent surface mesh). A particularly effective approach has been developed by David Goodsell and involves the use of surface representations where the level of detail can be dialed up or down depending on the distance to the camera (Goodsell, 2005). In terms of the data sets that guide our representations, we are also faced with the reality that we currently have little structural information between the molecular realm (nanoscale) and the cellular realm (micron scale). There is progress in techniques such as electron tomography that reveal with increasing resolution cell-wide surveys of molecular components and their cel-

lular geography (Marsh, 2005; Nickell et al., 2006). Super-resolution methods in optical microscopy are beginning to discern features beneath the theoretical diffraction limit of light and will soon give us new insights as well (Moerner, 2007). Although such techniques are beginning to close the knowledge gap, we are still searching for adequate ways to integrate these large data sets into visualizations.

Time is even more problematic than scale. Although animation is a powerful tool that lets one dissect the chronology and mechanism of a multistep process, how do we depict the variety of molecular motions that occur on drastically different timescales within a single movie? Thermal motion of individual atoms (10^{-15} to 10^{-12} s), amino acid side chain motions (10^{-9} s), diffusional events (10^{-6} s), transient conformational changes and folding (10^{-6} to 10^{-1} s), and large conformational changes all contribute to our understanding of molecular function. When one also considers the timescales relevant to processes in cell biology ($1 - 10^{2}$ s), we are faced with a daunting range spanning 17 orders of magnitude! Here again, the solution often lies in removing information that is not critical to communicate. The amplitude of motion that occurs over these timescales is often proportional to the speed of motion (that is, thermal motion occurs in the range of 0.001 to 0.1 Angstroms whereas conformational changes and folding events happen in the 1–100 Angstrom range). It may therefore be acceptable to leave out very rapid movements in shots depicting entire proteins but not in shots focused on active site chemistry where thermal motion, bond stretching, and bending remain important factors (Eisenmesser et al., 2005).

In addition to the fundamental design decisions discussed above, there also remain some very real technical software challenges to overcome. How does one actually animate a protein? One of the pioneering molecular movies to visualize a multiprotein assembly is Art Olson's animation of the Tomato Bushy Stunt Virus (TBSV)—an elegantly paced and choreographed sequence depicting the 3D structure of the virus and the conformational changes it undergoes at high pH (Table 1A). Although the morphing methods used in this movie are still used today and can help to visualize certain conformational transitions, a growing number of proteins do not lend themselves to such computations. Currently, if one has two or more PDB files of the same protein, it is possible to morph between these using interpolation techniques that calculate a possible trajectory through 3D space between the start and end positions of each atom in the PDB files (with energy minimization at each step) (Echols et al., 2003). The intermediate structures are output as a series of PDB files that are then visualized in programs like Chimera (Figure 2A; Pettersen et al., 2004). However, conformational changes that involve either partial refolding of the structure or significant secondary structure reassignments (such as α-helical transitions) cannot be visualized with standard molecular graphics software (Figure 2B). In the case of the α-helical transition of the gp41 surface glycoprotein of HIV, a mechanical driver of membrane fusion, we can import the PDB data for models of the process into 3D software and then use character animation techniques to create a custom morph (Figure 2C; Table 1B; see Movie S1, available online). Although this approach lacks the energy minimization calculations and other computational "checks" on the morphing structure, the resulting movie can still serve as a compelling visual model that summarizes our understanding of the process.

Although we are beginning to explore the unique capabilities of Hollywood's software for scientific visualization, the 3D animation process remains exceptionally painstaking. The entertainment industry has a well-documented and efficient production pipeline, populated with hundreds of artists, each of whom specializes in a specific area of production (concept art, storyboarding, modeling, rigging, animation, texturing, lighting, rendering, special effects, technical direction, etc.). Unlike the film editing process where one starts with a bounty of footage that is progressively winnowed down into a coherent movie, the 3D animation pipeline is so time consuming and resource intensive that every single frame has to be planned in advance. There are typically very few, if any, wasted frames in an animated 3D production. Although the scientific community has yet to expand its visualization workforce to that of Hollywood, advanced custom molecular visualizations still rely on the same labor-

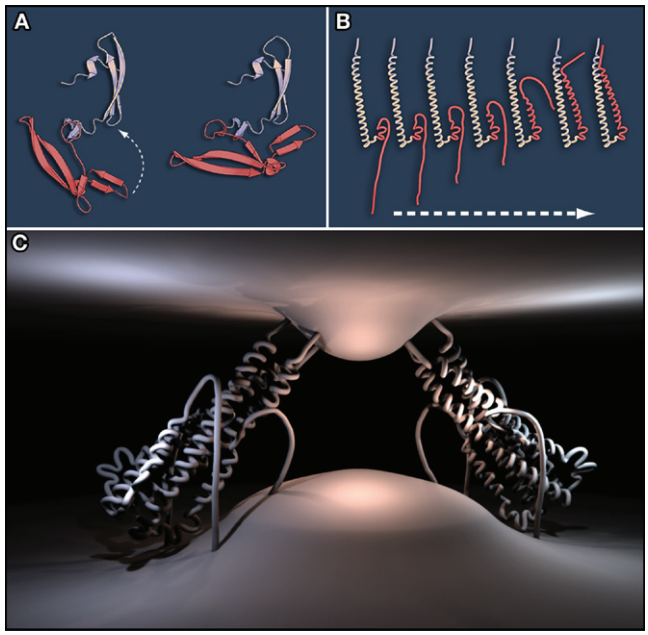

Figure 2. Approaches to Protein Morphing

Although many protein conformational morphs can be represented using linear interpolation techniques, certain types of domain motion or refolding are not amenable to such computations.

(A) Simple domain rotation in cyanovirin-N (from PDB ID. 1i5e → 1i5b)—the entire sequence of steps can be calculated using interpolation and downloaded from the Yale Morph Server (http://www.molmovdb.org/molmovdb/morph/).

(B) Example of a conformational change that is difficult to compute using interpolation. A morph sequence created in the 3D software Autodesk Maya using traditional character animation techniques. The gp41 of HIV undergoes an α-helical transition (partial structure of a single monomer is shown) during membrane fusion and viral entry.

(C) A frame from "HIV Entry: gp41-Mediated Membrane Fusion." The movie shows an animated version of the α-helical transition in (B) in the context of two gp41 trimers and the resulting cellular and viral membrane deformations (http://www.molecularmovies.com/movies/gp41_061008.html).

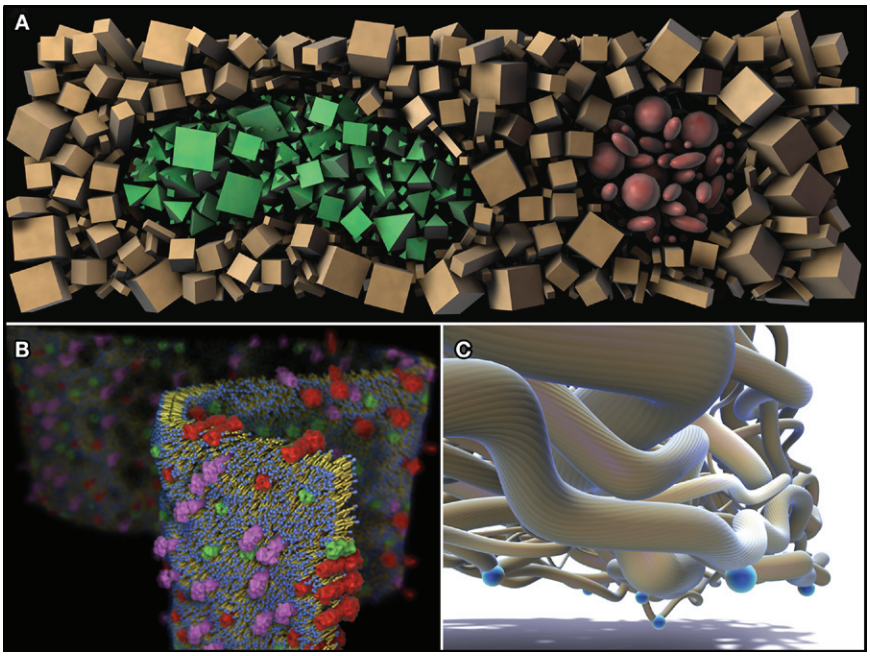

Figure 3. Automated Generation of Molecular and Cellular Environments
Three-dimensional modeling and animation software can be used as platforms to programmatically generate molecular and cellular environments with defined characteristics. These can subsequently be used as visual models for communication purposes, or physical simulations of cellular or molecular behavior. (A and B) Environments created by Graham Johnson using plugins he scripted for Maxon's Cinema 4D program. (A) The algorithm fills a volume (such as an organelle interior whose shape can be extracted from in vivo studies) with molecular surfaces, represented here as simple cubic, pyramidal, and spherical shapes according to a given distribution function. (B) A similar program places objects on a surface. Here, mock proteins surrounded by lipids form a ribbon of cell membrane. Figures courtesy of Graham Johnson.
(C) Model of acellular matrix ("ACM") created by Jason Sharpe and colleagues using Autodesk's Maya 3D program. Maya's Embedded Language (MEL) was used to generate individual stochastic particle trajectories with collision avoidance. These trajectories were then converted to NURBS curves and NURBS extrusions of various diameters (thick white fibers). Cells (blue spheres) are then seeded into this 3D model and their invasion behavior is simulated (http://cellmath.med.utoronto.ca/clips/LumsdenSig2005jpeg.mov). Figure courtesy of Nicholas Woolridge.

intensive production pipeline. Unless you are visualizing the direct output of a molecular dynamics simulation (Table 1C) or tomographic reconstruction (Table 1D and 1E), the majority of cell and molecular movies you have encountered were probably the result of a lone animator laboriously modeling and animating every single piece of geometry in the scene. But what if this image generation process could be derived directly from "rules" gleaned from structural and biological data and then used to drive geometry and motion within the program?

Graham Johnson, a member of Art Olson's Molecular Graphics Laboratory at The Scripps Research Institute in San Diego, is pioneering the development of new techniques to infuse the movie creation process with more data and less tinkering by animators. The process can be summarized in the following steps: (1) gather data about the cellular compartment of interest, (2) make a list of its components and model their geometry based on structural data, (3) create a script that places all components within this environment, and (4) set the system in motion using dynamics and collision detection. A powerful aspect of this approach is that most of these steps can be informed with new data as they become available. The initial positions of molecular components in the environment could eventually be driven by relevant tomography atlases (Nickell et al., 2006). Although the current implementation relies on simple collision detection between components, integrating forces like electrostatics within the system would lead to more realistic simulations. The dynamics of the system could also be simulated using a variety of computational techniques like Brownian dynamics. Combining these approaches within one platform (with the vast rendering amenities found in a high-end 3D software package like Maxon's Cinema 4D) should provide a powerful visual modeling and communication tool (Figures 3A and 3B). From a visual standpoint, one can think of this approach as an animated extension of the pencil and watercolor techniques David Goodsell uses to create his stunning images.

Another approach is exemplified by the work of Jason Sharpe, Nicholas Woolridge, and Charles Lumsden at the University of Toronto Biomedical Communications program (Sharpe et al., 2008). Using the commercially available Maya 3D modeling and animation software from Autodesk, they created a visual simulation of how cells invade the extracellular matrix. Modeling the matrix environment and seeding it with virtual cells is a stochastic process that is custom-scripted into the software using Maya's Embedded Language (MEL). Although the cells are subjected to hours of in silico invasion, the simulation tracks individual cell migration patterns and monitors various characteristics of their behavior. The advantage of implementing this kind of simulation in an established 3D package like Maya is that the results can be visualized using the software's extensive surfacing and rendering toolset, allowing the researchers to have complete flexibility in camera motion as the simulation unfolds. Both immersive camera techniques as well as cross-section views of the matrix are used to "film" the cells' invasive behavior (Figure 3C; Table 1F). As with Johnson's approach, the goal is to evolve these computational and visual models by layering in additional types of data—in this case, data describing the signal transduction machinery underlying the invasive behavior of cells. Using these techniques, the simulation and visualization process is one and the same. Simulation results are easily communicated in that they are embedded into the visual output of the model.

Future Directions... toward a "Visual Cell"

Historically, structural biology has provided us with snapshots of macromolecular structure and function. As we decipher the dynamics of proteins, their interactions

and precise locations within cells, we also demand that our visualizations keep up and include these newfound characteristics. Perhaps one of the more exciting roles visualization could play in this new synthesis would be to provide a platform for visual integration of these disparate data sets. From a practical standpoint, this integration would occur within a unified software environment where the data could be merged, compared, and contextualized (Figure 4). At the moment, however, this ideal software environment does not exist, and the toolset needed to create these more sophisticated visualizations does not lie in the hands of scientists. Showing a simple binding event between two proteins can be a challenge using today's molecular graphics packages. Although many interesting morphing movies have been created using these tools (and they have improved our understanding of protein flexibility), the software cannot create any surrounding cellular environments that would place the morph in the context of a signaling cascade or other cellular event. Aspects such as molecular crowding or the relative kinetics of different reactions, for example, cannot be addressed because the software only plays back a series of PDB files from one or a small number of proteins. Depicting the formation of a fatty acid vesicle (Table 1G), the mechanism of action of ATP synthase (Table 1H), the steps in reovirus entry (Table 1I, Movie S2), or the assembly of an apoptosome (Table 1J and 1K) is an almost unimaginable task using these simple molecular graphics tools. Investigators who study these processes are engaging 3D animators who can apply the entertainment industry's powerful suite of software tools. These leading animation and special effects packages are completely molecule-agnostic, but they do provide a considerable amount of programming flexibility.

It is time to define a "wish list" for a software platform that can handle the modern visualization challenges mentioned above. The most critical requirement is that the software will need to read and import datasets from different fields of research. It must also provide powerful scripting tools as well as integrated simulation capabilities. In addition to the now standard set of modeling, animation, and dynamics tools, the software needs to offer total rendering and therefore aesthetic flexibility. One strategic decision will be to assess whether these capabilities can be built onto existing 3D software, or whether a completely new software toolkit will need to be developed from the ground up. For now, the entertainment industry's existing 3D software packages are probably the best solution, despite their steep learning curve and the considerable time and cost investment required to become fluent in their use. There may also be other, less immediately obvious ways in which the industry's software development efforts can help molecular visualization. For example, adapting crowd simulation software could prove useful if the individual simulated "agents" (that is, individual members of a simulated crowd) can be reprogrammed as molecular protagonists. In the same way that the meeting of two crowd agents can trigger a specific behavior (like a handshake, for example), partner proteins (like a receptor and its ligand) could be made to react if a collision occurred between them. Real-time rendering of complex 3D scenes is commonplace in many of today's leading games, and one might imagine repurposing these gaming platforms to visualize and interact with large data sets.

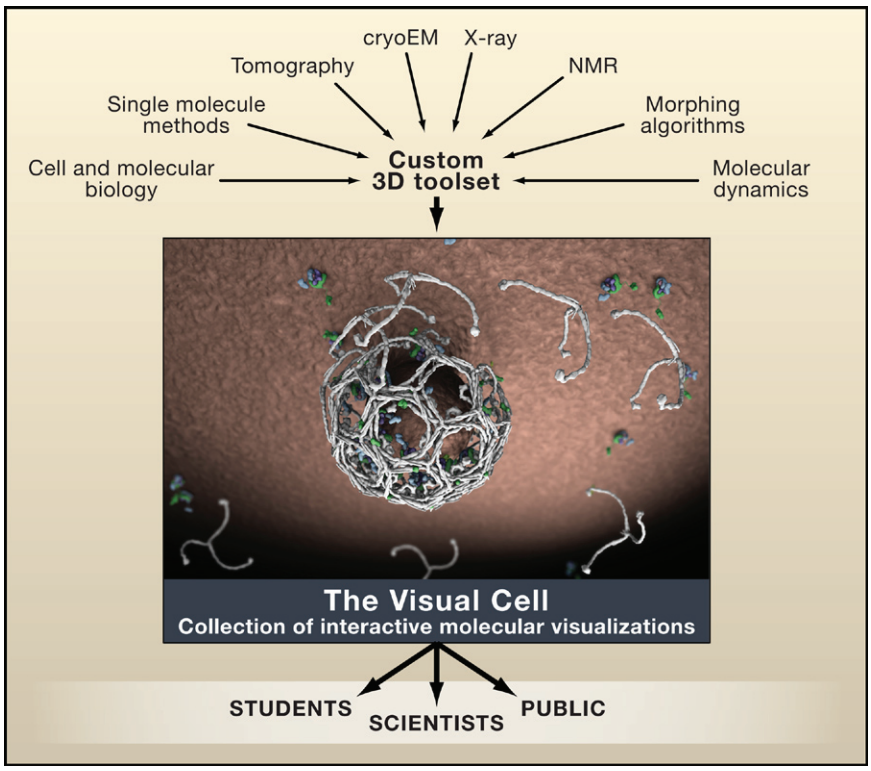

Figure 4. A Unique Opportunity for Data Integration and Visualization
The "Visual Cell" is a research and communication tool composed of numerous interconnected cell and molecular visualizations. Commercially available 3D software packages can be adapted and customized to read and import data from a variety of scientific research areas. Combined with the software's integrated physical simulation engine and image rendering toolkit, these datasets can serve as the foundation of accurate and interactive visualizations for a variety of audiences. Clathrin image courtesy of Janet Iwasa.

In some cases, collaborations between scientists and 3D animators have led to molecular movies of stunning quality and pedagogical value (Table 1L–1P). Still one might argue that many animations suffer from the communication gap between scientists and animators. Is the collaborative model a good one in the long term, or should we work toward simplifying animation tools to empower scientists to communicate their own results? As Hollywood notices that their professionally trained animators are expanding their lines of work into medical and scientific animation, scientists are becoming aware of the industry's robust suite of tools and choosing to learn them. Despite the availability of these sophisticated tools, will scientists have the time to engage in an otherwise very inten-

Table 1. Molecular Movie Links

A. Olson, A.J. (1981)	http://www.molecularmovies.com/movies/olson_TBSV.html
B. McGill, G. (2007)	http://www.molecularmovies.com/movies/gp41_061008.html
C. Martinez, G. (2007)	http://www.molecularmovies.com/movies/martinez_MD.html
D. Ortiz, J. (2006a)	http://www.molecularmovies.com/movies/ortiz_ribosomeAtlas.html
E. Ortiz, J. (2006b)	http://www.molecularmovies.com/movies/ortiz_EcoliCytoplasm.html
F. Sharpe, J., et al. (2005)	http://cellmath.med.utoronto.ca/clips/LumsdenSig2005jpeg.mov
G. Iwasa, J. (2007)	http://www.onemicron.com/quicktime/FA_denovo.mov
H. Sannuga, S. (2006)	http://www.molecularmovies.com/showcase/index.html#metabolic
I. McGill, G., and Iwasa, J. (2008)	http://www.molecularmovies.com/movies/mcgilliwasa_reovirus.html
J. Berry, D. (2007)	http://www.molecularmovies.com/movies/berry_apoptosis.html
K. Berry, D. (2008)	http://www.molecularmovies.com/movies/berry_malariaV4.html
L. Johnson, G. (2000)	http://www.fivth.com/fiVthSite/web-content/NewFiles/GrahamJcom/web-content/NewFiles/gjPortfComp/gjCBanim/1KinesinGrahamGarland.mov
M. Keller, E. (2003)	http://www.bloopatone.com/quicktimes/fold.mov
N. Keller, E. (2007)	http://www.bloopatone.com/quicktimes/SRP_web.mov
O. Martinez, G., and Davy, S. (2007)	http://www.hhmi.org/bulletin/may2007/chronicle/popups/molecules_1.html
P. XVIVO (2006)	http://multimedia.mcb.harvard.edu/anim_innerlife.html

sive design and programming process? Or rather, is it more likely that a new subdiscipline will emerge—one defined by a unique combination of training in scientific research, programming, graphic design, and advanced 3D software tools? Just as expert knowledge of the science and deft ability in PowerPoint do not necessarily make for successful presentations, dual-trained scientist-animators will also have to be effective teachers and storytellers. In many ways, they may need to be just as skilled as Pixar animators in the art of crafting their scientific stories.

Visualization has had a pervasive impact on our understanding and communication of the world around us. This was true of cave paintings, and it remains especially relevant in today's use of advanced computer graphics in structural biology. There are efforts to collect and organize existing cell and molecular biology visualizations that were created on an ad hoc basis to facilitate their dissemination and use in the classroom (http://www.molecularmovies.org; Table 1). A worthy common goal over the next few decades would be to commission and assemble a collection of visualizations that can be stitched together into a seamless (yet updatable) whole—a "Visual Cell" that reveals the beauty of the molecular inner workings of the cell. With advances in interactive computer graphics and input from the game industry, this cellular environment could be made to interact with its visitors and allow them to trigger their own visual simulations. This goal may also present a unique opportunity for systems and structural biology approaches to merge and draw on their respective strengths: quantitative modeling of signaling networks on the one hand, and detailed structural analysis of these networks on the other. Finally, a "Visual Cell" environment with the characteristics described above would be poised to become a splendid cell biology teaching tool. To use a Hollywood-inspired analogy, nature has handed us the most intricate and yet captivating script ever written. Casting is practically finished: our structural databases are bursting with protein actors, and the stage is set to begin creating an interactive experience of the cell. Now we just need a producer—but "production" depends on the willingness of the scientific community (and its funding agencies) to think of scientific visualization as an integral part of the research and discovery process.

Supplemental Data

Supplemental Data include two movies and can be found with this article online at http://www.cell.com/cgi/content/full/133/7/1127/DC1/.

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